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REVIEW ARTICLE

Angiogenesis drives psoriasis pathogenesis

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Summary

Psoriasis pathogenesis is closely associated with disease-inducing Th1 and Th17 cells. Yet, several studies suggest that aberrant keratinocyte or endothelial cell signalling significantly contributes to disease manifestation. Histological hallmarks of psoriatic skin include the infiltration of multiple immune cells, keratinocyte proliferation and increased dermal vascularity. Formation of new blood vessels starts with early psoriatic changes and disappears with disease clearance. Several angiogenic mediators like vascular endothelial growth factor, hypoxia-inducible factors, angiopoietins and pro-angiogenic cytokines, such as tumour necrosis factor (TNF), interleukin (IL)-8 and IL-17, are up-regulated in psoriasis development. Contact- and mediator-dependent factors derived from keratinocytes, mast cells and immune cells may contribute to the strong blood vessel formation of psoriasis. New technologies and experimental models provide new insights into the role of angiogenesis in psoriasis pathogenesis. Interestingly, many therapies target not only immune cells, but also protein structures of endothelial cells. Here we summarize the role of pro-angiogenic factors in psoriasis development and discuss angiogenesis as a potential target of novel therapies.

Keywords
psoriasis, angiogenesis, Th17

Psoriasis

Psoriasis is a chronic inflammatory disease of skin and small joints, which occurs in 2–4% of the Caucasian population (Ghoreschi *et al.* 2003a,b; Schon & Boehncke 2005), resulting in a severe impairment of quality of life. In more than 50% of the patients, psoriasis establishes within the first three decades of life. These patients tend to develop a chronic and severe course of disease. Psoriasis is characterized by the formation of sharply demarked erythematous plaques with large scaling (Figure 1). Plaque formation occurs mainly at sites of strong mechanical stress such as the sites of stretched skin or intertrigenes. Elbows, knees and scalp are involved in the majority of patients (Griffiths & Barker 2007). Histologically, chronic psoriasis plaques are characterized by typical changes in the epidermis and in the dermis (Schon & Boehncke 2005; Griffiths & Barker 2007). Epidermal findings include hyperproliferation of keratinocytes, leading to epidermal thickening and elongated rete ridges that form fingerlike protrusions into the dermis. The granular layer of the epidermis, the starting site of terminal keratinocyte differentiation, is strongly reduced or missing.

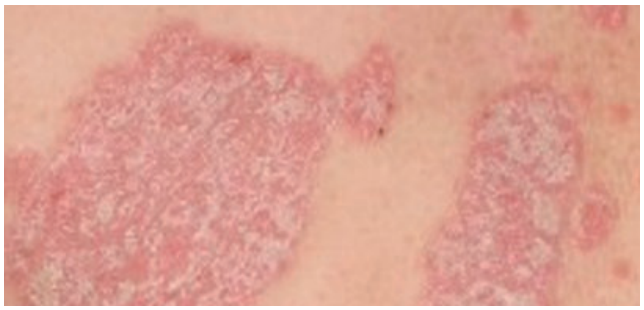

Figure 1 Clinical picture of psoriasis. Multiple psoriatic plaques on the back of a patient with chronic psoriasis.

The normally anuclear layer of cornified keratinocytes contains foci with nucleated keratinocytes, termed parakeratosis. The epidermis becomes infiltrated by neutrophils and activated $CD8^+$ T lymphocytes. Within the dermis, an inflammatory infiltrate composed of lymphocytes, macrophages, mast cells and neutrophils is observed (Figure 2). Elongated and dilated blood vessels in the dermal papillae represent a further histological hallmark of psoriatic skin lesions (Figure 3).

Initial steps in psoriasis pathogenesis: the unsolved riddle

Even though successful treatment regimens for the therapy of psoriasis have been established for a long time (Menter & Griffiths 2007), the cell type that is primarily responsible for the onset of the disease is still under debate. First investigations focused on keratinocytes. Aberrant activation and metabolism of epidermal keratinocytes, leading to strongly enhanced keratinocyte proliferation, are characteristic features of psoriatic skin (Van de Kerkhof & Van Erp 1996). In line with this, psoriatic skin has an eightfold shortened epidermal turnover due to increased keratinocyte proliferation (Weinstein *et al.* 1984). More recent studies show the association with altered expression of transcription factors of the activator protein-1 (AP-1) in keratinocytes in psoriasis-like skin lesions in experimental mice. In transgenic mice, deletion of the AP-1 family members JunB and c-Jun specifically in basal keratinocytes induces an inflammatory skin disease resembling psoriasis (Zenz *et al.* 2005), further emphasizing a critical role of keratinocytes in triggering psoriasis.

Together, current models suggest complex interactions between keratinocytes and cells of the immune system as initial steps in psoriasis pathogenesis (Elder *et al.* 1989; Christophers 1996; Nickoloff & Nestle 2004; Lowes *et al.*

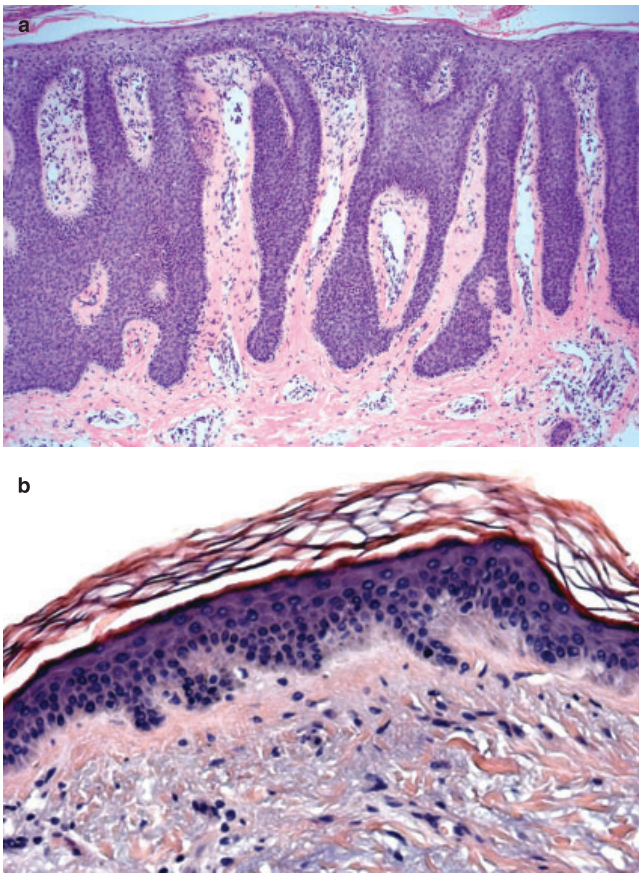

Figure 2 Psoriasis histology. (a) H&E staining of psoriasis skin. Epidermal thickening with elongated rete ridges. Infiltration of neutrophils in the corneal layer. Lymphocytic infiltrate, few macrophages and mast cells in the dermis. Dilated and elongated capillaries in the papillary dermis. (b) Healthy skin with regular epidermis and orthokeratosis.

2007; Nickoloff 2007; Rebholz *et al.* 2007). In transgenic mice, ubiquitous activation of the transcription factor NFκB, which is a potent inducer of inflammatory responses, leads to the development of a psoriasis-like skin disease, including acanthosis, hyperkeratosis, parakeratosis and dilatation of dermal blood vessels (Rebholz *et al.* 2007). This phenotype is dependent on the simultaneous NFκB activation in keratinocytes and T cells, as selective activation of the transcription factor either in keratinocytes or in T cells alone is not sufficient to induce the pathogenic changes. This recent report underlines the importance of keratinocyte–T-cell interactions in the pathogenesis of psoriasis. T cells and Langerhans cells infiltrate the epidermis where they are in direct contact with keratinocytes. Mediators secreted by mononuclear cells infiltrating the dermis are capable of inducing the proliferation of keratinocytes and endothelia.

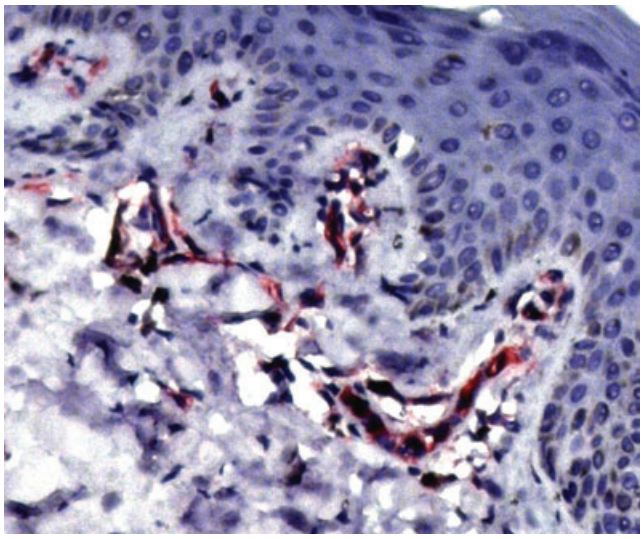

Figure 3 Blood vessels in psoriatic lesion. Tortous dermal capillaries stained with anti-CD31 antibody (red).

The dermis of psoriatic skin is infiltrated predominantly by CD4-positive T-helper (Th) cells, which produce pro-inflammatory cytokines such as interferon (IFN)-γ, TNF and IL-17 (Ghoreschi *et al.* 2003a,b, 2007). Also, elevated levels of IL-6, IL-8 and keratinocyte growth factor [transforming growth factor-α (TGF-α)] are found in psoriatic lesions (Schroder & Christophers 1986; Elder *et al.* 1989; Christophers 1996). Thus, an intense cross-talk between immune cells and keratinocytes seems to establish an interactive cytokine network, responsible for the development of psoriasis.

Psoriasis is considered to be an inflammatory autoimmune disease, even though the psoriasis-inducing autoantigen is not known. For many years, psoriasis and other inflammatory organ-specific autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, were thought to be orchestrated only by IFN-γ-producing Th1 cells (Schlaak *et al.* 1994; Ghoreschi & Rocken 2003). In early psoriatic lesions, the dermis is mainly infiltrated by $CD4^+$ Th cells, which produce IFN-γ and IL-17, but no IL-4 or IL-10 (Teunissen *et al.* 1998; Ghoreschi *et al.* 2003b; Wilson *et al.* 2007). Systemic treatment with cyclosporine A, which impairs cytokine production and activation of T lymphocytes, improves psoriasis (Mueller & Herrmann 1979). The essential role of T cells in promoting psoriasis was further supported by clinical observations from psoriasis patients with haematological malignancy, who cleared or obtained long-term remission after the transplantation of bone marrow from healthy donors without a history of psoriasis (Kanamori *et al.* 2002). On the other hand, some patients developed psoriasis for the first time after the transplantation of bone marrow from donors with psoriasis (Snowden & Heaton 1997). In line with this, psoriasis therapy with monoclonal antibodies (mAbs) directed against the CD4 molecule, but not with mAbs targeting the CD8 molecule, improves psoriasis (Nicolas *et al.* 1991; Prinz *et al.* 1991; Gottlieb *et al.* 2000). Similarly, skin xenograft models on SCID mice revealed that populations including autologous IFN-γ-producing CD4 T cells could induce psoriasis in healthy skin grafts from patients with a history of psoriasis, whereas adoptive transfer of $CD8^+$ T cells from the same patient could not induce the disease (Nickoloff & Wrone-Smith 1999). As this approach suggested that IFN-γ-producing Th1 cells are capable of inducing psoriasis, we designed a study where psoriasis patients were treated with the Th2-inducing cytokine IL-4. Indeed, IL-4 deviated the skin cytokine pattern from an IL-4-deficient Th1/Th17 phenotype into an IL-4-dominated milieu and dramatically improved the disease (Ghoreschi *et al.* 2003a,b). Thus, clinical investigations and experimental studies all indicate that IFN-γ-producing Th1 cells and IL-17-producing Th17 cells are central for causing psoriasis (Fitch *et al.* 2007; Ghoreschi *et al.* 2007; Wilson *et al.* 2007; Zaba *et al.* 2008).

Recent studies underlined this by showing the concomitant presence of both IFN-γ-producing Th1 cells and IL-17-producing Th17 cells (Austin *et al.* 1999; Ghoreschi *et al.* 2003b). The strong co-expression of the Th17-cell-promoting cytokine IL-23 and the Th17-associated cytokine IL-22 in psoriatic skin further supported that both Th1- and Th17-cell subsets are causally involved in the manifestation of psoriasis (Lee *et al.* 2004; Wilson *et al.* 2007; Zheng *et al.* 2007). As it is thus likely that psoriasis is a Th1/Th17-cell-mediated inflammatory autoimmune disease, a mAb that targets and neutralizes IL-12/IL-23 p40, a subunit shared by IL-12 and IL-23, was investigated on the therapy of psoriasis. Indeed, this mAb dramatically improves psoriasis and prevents Th1 and Th17 cell development (Toichi *et al.* 2006; Krueger *et al.* 2007). As IL-4 has been shown *in vitro* to inhibit both Th1 and Th17 differentiation, IL-4 may also suppress IL-17 in psoriasis patients (Ghoreschi *et al.* 2003b; Harrington *et al.* 2005; Weigert *et al.* 2008). Indeed, we found that a closely related cytokine, IL-19, is suppressed by IL-4 therapy *in vivo* (Ghoreschi *et al.* 2003b). Even improving psoriasis with an anti-TNF mAb reduces Th17 and Th1 cytokines at the site of psoriasis lesions (Zaba *et al.* 2007).

To maintain the inflammation in psoriasis, the disease-inducing Th1 and/or Th17 cells may either proliferate *in situ* or transmigrate from the periphery into their target

organ, the dermis. This process depends on close interaction of inflammatory Th1/Th17 cells with the vascular bed. The interaction between the lymphocyte function-associated antigen-1 (LFA-1) on lymphocytes and ICAM-1 (intercellular adhesion molecule-1) on endothelial cells (EC) mediates the firm adhesion of leukocytes to the endothelium, a prerequisite for extravasation. Under inflammatory conditions, ICAM-1 is strongly induced on the vascular endothelium. Efalizumab, a humanized mAb against the alpha-subunit of LFA-1, interferes with the binding of LFA-1 to ICAM-1. In consequence, blocking the binding of LFA-1 to ICAM-1 inhibits the transmigration of T cells and results in slow resolution of the skin disease. Efalizumab that strongly improves psoriasis in 25–30% of patients with stable plaque psoriasis thus became one of the approved therapies for psoriasis with biologics (Hodulik & Hadi 2006; Schon 2008). Patients usually develop lymphocytosis during Efalizumab therapy, further suggesting that Efalizumab therapy prevents emigration of disease-inducing T lymphocytes. Moreover, targeting T-cell–EC interactions by Efalizumab suggests a complex interaction between immune response, inflammation and angiogenesis. Immune responses and inflammation are established inducers of angiogenesis, whereas angiogenesis promotes and maintains immune and inflammatory processes (Miotla *et al.* 2000; De Bandt *et al.* 2003; Watanabe *et al.* 2004; Kneilling *et al.* 2007).

Angiogenesis in psoriasis may not only be a cofactor but also an inducer of psoriasis development. Changes of the superficial microvasculature during psoriasis result in an angiogenic phenotype. Pro-angiogenic mediators, such as TNF, vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF), IL-8 or angiopoietins, are enriched in psoriatic skin (Creamer *et al.* 2002; Heidenreich *et al.* 2008). A pro-angiogenic role has also been attributed to the Th17 cytokine IL-17 (Starnes *et al.* 2001; Numasaki *et al.* 2003). As angiogenesis is tightly regulated by a balance between pro-angiogenic and anti-angiogenic stimuli, the expression of anti-angiogenic factors should also be modulated during psoriasis. Indeed, keratinocytes isolated from psoriatic skin show a strongly reduced expression of thrombospondin-1 (TSP-1), an endogenous inhibitor of angiogenesis. TSP-1 suppresses EC proliferation and migration, neovessel formation and tumour growth (Tolsma *et al.* 1993; Boukamp *et al.* 1997; Streit *et al.* 1999). In healthy skin, secretion of TSP-1 by basal keratinocytes obviously helps to maintain the separation between the vascular dermis and the avascular epidermis (Wight *et al.* 1985; Detmar 1996). Together, these findings suggest the involvement of angiogenesis in psoriasis pathogenesis.

Before discussing various possible roles of angiogenesis in the psoriasis pathogenesis, we will summarize important physiological mechanisms leading to blood vessel formation and methods needed for analysing angiogenesis *in vitro* and *in vivo*.

Angiogenesis

The formation of new capillaries from pre-existing blood vessels is described as angiogenesis. It is essential for embryogenesis but is almost lacking in most adult tissues. Angiogenesis occurs in at least two different ways: (i) sprouting of new capillaries from pre-existing blood vessels and (ii) non-sprouting angiogenesis or intussusception, the dividing of pre-existing vessels by transcapillary pillars (Risau 1997; Carmeliet 2000).

Sprouting angiogenesis is initiated by the activation of vascular EC through several factors such as VEGF or basic fibroblast growth factor (bFGF). The following steps of angiogenesis include vasodilatation, increased vascular permeability, destabilization of existing blood vessels, degradation of the extracellular matrix (ECM), EC proliferation and migration, lumen formation and vessel maturation by recruiting perivascular supporting cells (Klagsbrun & Moses 1999; Carmeliet 2003). Increased vascular permeability leads to leakage of plasma proteins, which provide a provisional matrix for migrating EC that, in addition, requires the degradation of the ECM by proteases such as matrix metalloproteinases (MMPs) and plasminogen activators. It further requires transient destabilization of blood vessels by dissolving interendothelial and periendothelial cell contacts. ECM degradation also leads to the release of pro-angiogenic factors (VEGF, bFGF, IGF-1 (insulin-like growth factor) stored in the ECM, thereby promoting angiogenesis. Migration of EC is directed by a gradient of angiogenic mediators and involves the expression of integrins, cell-adhesion molecules on the EC surface, which interact with components of the ECM. The newly formed, immature cord-like structures then acquire a lumen and mature by the recruitment of supporting cells such as pericytes or smooth muscle cells. In mature, stabilized blood vessels, EC are able to survive for several years.

Angiogenesis is tightly regulated by a balance between pro- and anti-angiogenic mediators. Physiological angiogenesis is induced only transiently during processes such as wound healing, pregnancy or the female reproductive cycle. Pathological angiogenesis occurs under conditions such as tumour growth and chronic inflammation, as observed during rheumatoid arthritis or psoriasis. In these conditions, angiogenesis is needed for disease development (Folkman

1995; Kneilling *et al.* 2007; Heidenreich *et al.* 2008; Muller-Hermelink *et al.* 2008; Wieder *et al.* 2008).

Methods for the analysis of angiogenesis

A variety of different *in vivo* and *in vitro* methods are available for the investigation of vessels and vessel formation in health and disease (Staton *et al.* 2004) (Table 1). In principle, non-invasive and invasive techniques can be distinguished. Non-invasive techniques include laser Doppler fluxmetry and native video-capillaroscopy in humans. Intravital multi-fluorescence microscopy and positron tomography (PET) analysis in small animals after injection of radiolabelled peptides represent powerful tools to analyse the vasculature and angiogenesis in the natural environment. Laser Doppler fluxmetry allows analysing cutaneous microvascular haemodynamics, whereas morphological parameters of the superficial microvasculature of the skin can be studied using native video-capillaroscopy (Hern & Mortimer 1999). Intravital multi-fluorescence microscopy can be used for quantitative estimation of microcirculation, angiogenic processes and microhaemodynamic parameters of healthy and tumour tissues (Vajkoczy *et al.* 1998). Transparent chambers, which are surgically implanted into laboratory mice, allow the *in vivo* visualization of even individual tumour blood vessels. Blood vessels can also be visualized *in vivo* using radiolabelled cyclic peptides containing the amino acid sequence arginine–glycine–aspartate (RGD peptides), the binding motif for the integrin $\alpha_V\beta3$. On EC, $\alpha_V\beta3$ is strongly up-regulated during angiogenesis, whereas it is expressed only at low levels on quiescent endothelium. After injection of radiolabelled RGD peptides, animals can be analysed *in vivo* using PET (Pichler *et al.* 2005; Kneilling *et al.* 2007; Muller-Hermelink *et al.* 2008).

Invasive techniques include biopsies for histology or histochemistry and visualization of intact blood vessels in animal models by intravenous injection of fluorescent lectins (Thurston *et al.* 1996) or endothelium-specific antibodies (Corada *et al.* 1999). Histology allows the analysis using light microscopy (LM), immunohistology or electron microscopy (EM). LM unravels cellular organization and morphology and still allows a most reliable quantification of the expansion of the superficial dermal microvasculature also in human disease such as psoriasis. More detailed information on the ultrastructural level can be obtained by EM, allowing high magnifications. Thus, the detection of the change of the normal arterial capillary loops in the dermal papillae into a venous phenotype in psoriatic skin required the resolution of standard EM. The elongated superficial microvasculature in psoriatic lesions can be characterized by antibodies binding to endothelium-specific markers, such as PECAM-1 (CD31) or Meca-32 (CD34). Immunohistochemistry of tissue

Table 1 Methods to analyse vascular biology

Method	Analysed parameters	Application
Laser Doppler fluxmetry	Cutaneous microvascular haemodynamics	Humans and animal models; non-invasive
Native video-capillaroscopy	Morphological parameters of the superficial microvasculature of the skin	Humans and animal models; non-invasive
Intravital multi-fluorescence microscopy	Quantitative estimation of microcirculation, angiogenic processes and microvascular haemodynamics	Animal models; non-invasive
Small animal positron tomography	Quantitative analysis of angiogenic blood vessels	Animal models; non-invasive
Light microscopy	Cellular organization and the morphology of a given tissue by staining with different dyes	Tissue sections of biopsies; invasive
Electron microscopy	Cellular ultrastructure	Ultrathin tissue sections of biopsies; invasive
Immunohistochemistry	Identification of distinct cell types or *in situ* expression analysis of proteins on tissue sections by specific antibodies	Tissue sections of biopsies; invasive
Intravenous injection of fluorescent-labelled lectins or endothelium-specific antibodies	Intact blood vessels within their tissue context	Animal models, invasive
Enzyme-linked immunosorbent assay	Secreted pro- or anti-angiogenic mediators in serum or tissue homogenates	Humans and animal models; invasive
Spheroid-based sprouting assay	Pro-/anti-angiogenic activity of distinct compounds	Three-dimensional *in vitro* angiogenesis assay
Sphere assay	Pro-/anti-angiogenic activity of distinct compounds	Three-dimensional *in vitro* angiogenesis assay
Aortic ring assay	Pro-/anti-angiogenic activity of distinct compounds	Three-dimensional *ex vivo* angiogenesis assay

sections showed that both keratinocytes and mast cells are potential producers of pro-angiogenic mediators, such as VEGF, bFGF or IL-8 (Detmar *et al.* 1994; Biedermann *et al.* 2000; Sayed *et al.* 2008). In contrast to immunohistochemistry, the intravenous injection of fluorescent-labelled lectins or endothelium-specific antibodies allows the analysis of intact blood vessels within their tissue context. Lectins mark the luminal surface of EC, whereas the specific antibodies bind to proteins on the endothelial surface, which is subsequently analysed by histology. Enzyme-linked immunosorbent assay (ELISA) and Western blotting are used to quantify the amount of secreted pro- or anti-angiogenic mediators in serum or tissue homogenates. ELISA methods were used to demonstrate high levels of VEGF and of plasminogen activator inhibitor-1 in sera of psoriasis patients.

The pro- or anti-angiogenic activity of proteins determined by the methods above can be tested either by three-dimensional *in vitro*, *ex vivo* or *in vivo* angiogenesis models. For *in vitro* assays, either collagen-embedded EC spheroids or fibrinogen-embedded microbeads coated with EC are used. The *ex vivo* assay is based on collagen-embedded rat or mouse aortic rings. Pro-angiogenic activity can be tested as the outgrowth of EC sprouts and the inhibition of sprouts induced by VEGF is used to characterize anti-angiogenic activities.

To verify pro- or anti-angiogenic properties *in vivo*, the cornea micropocket assay or the chicken chorioallantois membrane (CAM) assay are commonly used. For the cornea assay, pellets containing the substance to be analysed are surgically implanted in the physiologically avascular cornea of rabbits, rats or mice. Pro-angiogenic activity will lead to the ingrowth of newly formed capillaries towards the pellet starting from the limbal artery. Using this assay, pro-angiogenic signals were identified in a conditioned medium of keratinocytes isolated from psoriasis patients (Nickoloff *et al.* 1994). By using the CAM assay, which is performed in the chicken egg, vascularization of the CAM during embryogenesis is analysed after methylcellulose pellets, including the substance to be tested, are placed onto the CAM for distinct incubation times. Several other methods that cannot all be described here exist. Based on the techniques described, the microvascular pattern of psoriasis has been intensively studied.

Microvascular changes in the papillary dermis of psoriatic plaques

Psoriasis starts with angiogenesis in the superficial dermal microvasculature. Dermal papillary capillaries increase in tortuosity, dilatation and permeability, and show prominent elongation (Figure 3) (Telner & Fekete 1961; Ragaz & Ackerman 1979; Braverman & Sibley 1982). These morphological changes occur prior to visible epidermal hyperplasia (Telner & Fekete 1961; Kulka 1964). The vascular changes during early stages of psoriasis pathogenesis closely correlate with enhanced cutaneous blood flow (Hull *et al.* 1989) even in the neighbouring perilesional, clinically unaffected skin (Goodfield *et al.* 1994). EM shows ultrastructural changes of the capillary loops in the dermal papillae. Whereas in normal skin, capillary loops show an arterial phenotype, they exhibit characteristic features of venous capillaries such as a single or multilayered basement membrane and bridged fenestrations of the endothelium in psoriasis plaques (Braverman & Yen 1977). Following successful therapy, venous capillary loops return to arterial capillaries (Braverman & Yen 1977). Normalization of the superficial microvascular dermal plexus proceeds normalization of the epidermal structure (Braverman & Sibley 1982). Besides the morphological changes, the papillary dermal microvessels in psoriatic lesions show an increased expression of inflammation-associated adhesion molecules such as E-selectin, ICAM-1 and vascular cell-adhesion molecule-1. These adhesion molecules allow tethering and firm adhesion of leukocytes to the endothelium (Springer 1994), important requirements for lymphocyte extravasation and the establishment of an inflammatory response.

Proliferation and migration are main characteristics of angiogenic EC; EC of psoriasis plaques show enhanced proliferation as determined by autoradiography (Braverman & Sibley 1982; Morganroth *et al.* 1991) and immunohistochemistry (Creamer *et al.* 1997). In order to migrate, EC utilize temporary contacts to components of the ECM, which are mediated by integrins expressed on the EC surface. Integrins are heterodimeric transmembrane proteins that activate intracellular signalling pathways upon ligation with the corresponding ligands. Several integrins modulate the pro-angiogenic response (Jin & Varner 2004). Among these integrins, $\alpha_V\beta3$ is expressed at only low levels on quiescent vasculature. The $\alpha_V\beta3$ integrin functions as EC receptor for von Willebrand factor, fibrinogen and fibronectin (Cheresh 1987). During angiogenesis, endothelial $\alpha_V\beta3$ expression is strongly up-regulated whether it results from inflammation or from tumour growth (Brooks *et al.* 1994a,b; Kneilling *et al.* 2007; Muller-Hermelink *et al.* 2008). The inhibition of angiogenesis *in vivo* by peptide or mAb antagonists of $\alpha_V\beta3$ underlines its important role in neovascularization (Brooks *et al.* 1994a,b). Also in psoriasis, increased $\alpha_V\beta3$ expression on EC is observed. Thus, the superficial microvasculature of lesional psoriatic skin shows enhanced $\alpha_V\beta3$ levels compared with healthy skin (Creamer

& Barker 1995; Nickoloff 2000). In summary, the current data strongly favour angiogenesis to be responsible for the extension of the superficial dermal microvasculature in psoriasis.

Pro-angiogenic factors in psoriatic skin

As angiogenesis is one of the key features of psoriasis, various studies focused on the identification of pro-angiogenic mediators in psoriatic skin. Evidence for keratinocyte-derived pro-angiogenic signals came from a study comparing the angiogenic activity of conditioned media (CM) from keratinocytes isolated from either lesional or non-lesional skin of psoriasis patients (Nickoloff *et al.* 1994). CM from lesional or non-lesional keratinocytes stimulated EC migration *in vitro* and showed strong angiogenic activity in the rat cornea micropocket assay *in vivo*. In contrast, CM from keratinocytes of healthy donors showed no pro-angiogenic response. Detailed search for the pro-angiogenic mediator revealed a large spectrum of pro-angiogenic factors, including VEGF, HIFs, angiopoietins, TNF, TGF-α, IL-8 and IL-17 (Figure 4).

Vascular endothelial growth factor

Vascular endothelial growth factor and its high-affinity tyrosine kinase receptors VEGFR-1 (Flt-1) and VEGFR-2 (KDR in humans/Flk-1 in mice) are essentially involved in vascular embryogenesis and adult neovascularization. VEGF, first described as vascular permeability factor (Keck *et al.* 1989), represents in its active form a homodimeric glycoprotein of 40–45 kDa. In mammals, seven different splice variants with pro-angiogenic properties and five different splice variants with anti-angiogenic functions are known (Harper & Bates 2008). VEGFR-1 or -2 are primarily expressed by vascular EC. VEGF binding to either of these receptors leads to

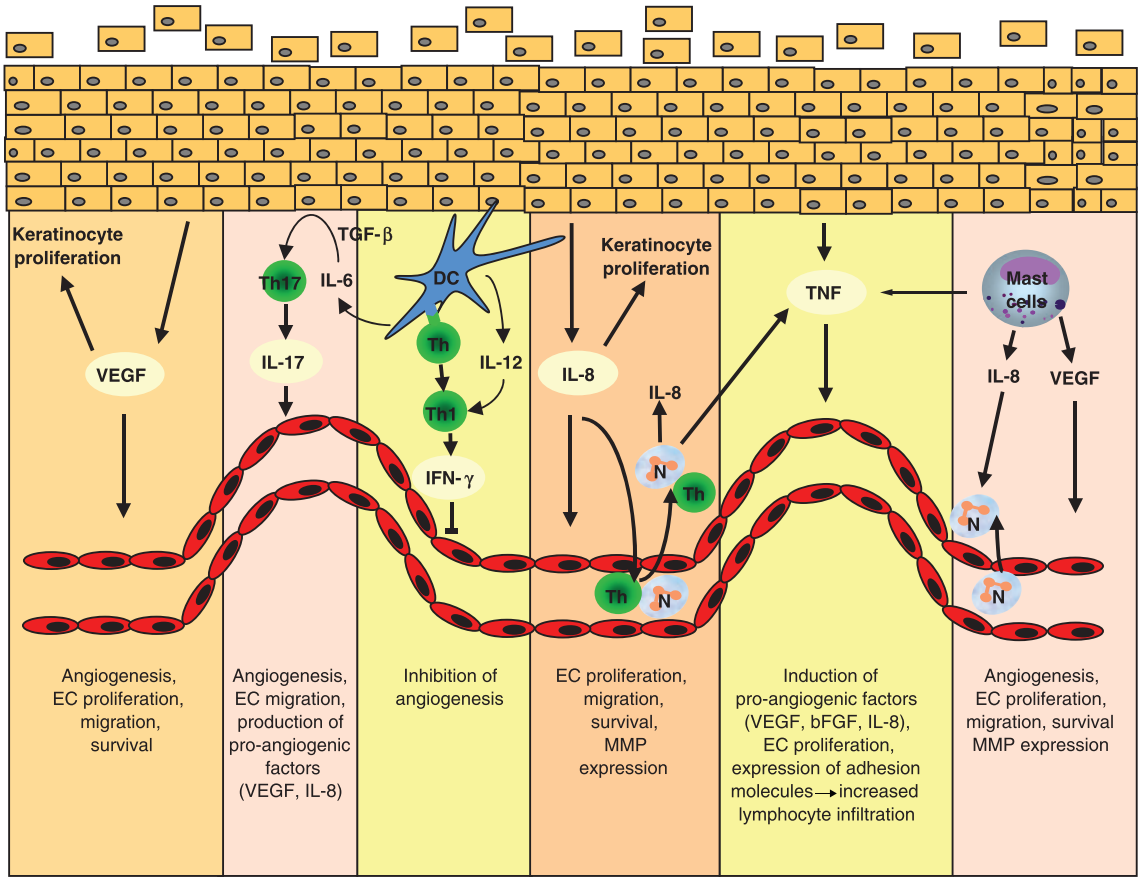

Figure 4 The role of angiogenesis in the pathogenesis of psoriasis. VEGF, vascular endothelial growth factor; IL, interleukin; IFN, interferon; TNF, tumour necrosis factor; TGF, tumour growth factor; MMP, matrix metalloproteinases; bFGF, basic fibroblast growth factor; ECs, endothelial cells; DC, dendritic cells; Th, T-helper cells; N, neutrophils.

receptor activation and intracellular signal transduction (De Vries *et al.* 1992; Shibuya 1995; Shibuya & Claesson-Welsh 2006). Yet, VEGF-induced proliferation, migration, survival and enhanced vascular permeability are mainly transduced by VEGFR-2 (Ferrara *et al.* 2003).

Vascular endothelial growth factor-induced angiogenesis seems to contribute to the pathogenesis of psoriasis. *In situ* hybridization and immunohistology show strong up-regulation of VEGF mRNA and protein expression in epidermal keratinocytes and enhanced expression of VEGFR-1 and -2 on EC of the dermal papillae (Detmar *et al.* 1994). As TGF-α induces VEGF expression and secretion by epidermal keratinocytes *in vitro* (Detmar *et al.* 1994) and is overexpressed in suprabasal keratinocytes of psoriatic skin, TGF-α might be responsible for the epidermal VEGF up-regulation during psoriasis.

Sera from patients with psoriasis have enhanced VEGF levels. Moreover, serum-VEGF levels correlate with disease severity (Creamer *et al.* 1996; Bhushan *et al.* 1999; Nielsen *et al.* 2002). In addition, single nucleotide polymorphisms of the VEGF gene strongly correlated with psoriasis pathogenesis (Young *et al.* 2004, 2006), suggesting that VEGF represents a modifier gene in the aetiology of psoriasis.

The pathophysiological role of VEGF in the induction of psoriasis was tested with transgenic mice overexpressing VEGF in keratinocytes (Detmar *et al.* 1998; Xia *et al.* 2003). VEGF overexpression selectively in basal keratinocytes (K14VEGF) resulted a chronic skin inflammation with enhanced numbers of tortuous capillaries, expressing increased levels of VEGFR-1 and -2, elevated numbers of mast cells in the upper dermis and increased leukocyte rolling and adhesion (Detmar *et al.* 1998). Older K14VEGF animals spontaneously develop an epidermal skin disease sharing many characteristic features with psoriasis including inflammatory infiltrates composed of $CD4^+$ T cells, mast cells and macrophages, and changes of the superficial dermal microvasculature (Xia *et al.* 2003). Transgenic mice treated with the VEGF antagonist VEGF-trap remain healthy, further supporting a central role of VEGF on causing skin inflammation.

Besides its potential role in causing aberrant angiogenesis in the upper dermis, VEGF may also contribute to keratinocyte proliferation and epidermal barrier homeostasis (Man *et al.* 2006; Elias *et al.* 2008). Thus, VEGFR-1 and -2 are detectable in lesional psoriasis skin (Man *et al.* 2006). As VEGF induced increased VEGFR expression by keratinocytes *in vitro* and VEGF expression is up-regulated by epidermal keratinocytes, VEGF may also contribute to keratinocyte proliferation in an autocrine manner. Psoriasis can be induced by external injury (Koebner phenomenon) and interestingly disruption of the epidermal barrier homeostasis induces VEGF expression (Elias *et al.* 2008). Transgenic mice deficient in epidermal VEGF expression have delayed permeability barrier recovery after acute perturbation, decreased density of dermal blood vessels and lack epidermal hyperplasia as well as angiogenesis in response to sustained barrier disruption (Elias *et al.* 2008). Thus, physiological production of VEGF obviously contributes to the normal proliferation, differentiation and functioning of the epidermis.

Hypoxia-inducible factors

The cardiovascular system is essentially required for sufficient supply of oxygen and nutrients. Therefore, low oxygen tension is a main inducer of angiogenesis. HIFs initiate the metabolic response to decreased oxygen tension. HIFs represent heterodimeric transcription factors composed of a constitutively expressed β subunit (aryl hydrocarbon receptor nuclear translocators: ARNT, ARNT2, ARNTL) and a regulatory α subunit (HIF-1α, HIF-2α, HIF-3α) (Harris 2002; Maxwell & Ratcliffe 2002; Wenger 2002). At physiological oxygen tension, the HIF-α subunits are continuously synthesized and degraded by the proteasome. For degradation, prolyl residues of the HIF-α subunits are hydroxylated by prolyl hydroxylases, which are active only in the presence of normal oxygen concentrations. The hydroxylated form is then recognized by the Von Hippel–Lindau (VHL) tumour suppressor protein leading to HIF-α ubiquitinylation and proteasomal degradation. Under hypoxic conditions, prolyl hydroxylases are inactive. In consequence, HIF-α subunits are no longer degraded and the increasing HIF concentrations lead to nuclear translocation. Among the HIF target genes are main regulators of angiogenesis such as VEGF (Levy *et al.* 1995; Liu *et al.* 1995; Forsythe *et al.* 1996), VEGFR-1 (Takeda *et al.* 2004), VEGFR-2 (Elvert *et al.* 2003), IL-8 (Kim *et al.* 2006) and Tie-2 (Tian *et al.* 1997).

In psoriasis lesions, HIF-1α and -2α expressions are increased (Rosenberger *et al.* 2007). In epidermal keratinocytes, HIF-1α colocalizes with VEGF expression, whereas HIF-2α is expressed in the epidermis and in dermal capillaries. Epidermal hypoxia and increased HIF expression may result from the strong epidermal proliferation and the enhanced metabolic demands. In addition, VHL mRNA and protein expression are decreased (Tovar-Castillo *et al.* 2007).

Angiopoietins

Besides the VEGF/VEGFR signal transduction system, the angiopoietins, Ang-1 and Ang-2, and their receptor Tie-2, a

receptor tyrosine kinase, are crucially involved in angiogenic processes. The Ang–Tie-2 system is essential for the growth, maturation and stabilization of blood vessels (Dumont *et al.* 1994; Sato *et al.* 1995; Davis *et al.* 1996; Suri *et al.* 1996; Maisonpierre *et al.* 1997). Ang-1 induces Tie-2 phosphorylation upon binding and activation of intracellular signal transduction cascades, leading to vessel stabilization and maintenance during vascular embryogenesis (Suri *et al.* 1996). In adult tissues, the low-level constitutive Tie-2 activation is thought to maintain the mature quiescent status of the resting endothelium (Wong *et al.* 1997). In contrast, Ang-2 antagonizes Tie-2 activation, causes vessel destabilization (Maisonpierre *et al.* 1997) and thus sensitizes existing blood vessels for growth or survival signals. In the absence of pro-angiogenic stimuli, Ang-2 obviously leads to vessel regression, but in the presence of pro-angiogenic signals to angiogenesis.

The Ang–Tie-2 system is activated during psoriasis (Kuroda *et al.* 2001; Voskas *et al.* 2005). Ang-1, Ang-2 and Tie-2 are all induced in the papillary dermis of psoriasis skin (Kuroda *et al.* 2001). Ang-1 is expressed in fibroblasts, mononuclear cells or DC, while Ang-2 expression seems to be confined to EC. The prominent reduction of Ang-2 expression after successful therapy suggests an important role of Ang-2 during angiogenesis in psoriasis (Kuroda *et al.* 2001).

The crucial contribution of Tie-2 signalling to skin inflammation was demonstrated in a transgenic mouse model (Voskas *et al.* 2005). Conditional overexpression of Tie-2 leads to a skin disease reflecting several characteristics of psoriasis such as epidermal hyperplasia, hyperkeratosis, parakeratosis and inflammatory infiltrates of predominantly lymphocytes, macrophages and mast cells and increased dermal vascularization. Repression of transgenic Tie-2 expression completely reversed the disease.

Besides its role in angiogenesis, Ang-2 sensitizes EC to inflammatory signals such as TNF by influencing TNF-induced expression of ICAM-1 and VCAM-1 on EC in an autocrine fashion, thereby facilitating leukocyte adhesion and infiltration (Fiedler *et al.* 2006). Therefore, Ang-2 might contribute to the inflammatory response during the development of psoriasis.

Cytokines

Several cytokines exhibit a profound impact on angiogenesis by influencing EC proliferation, migration or survival, or by modulating the expression of pro- or anti-angiogenic factors. Among the cytokines with pro-angiogenic activity, TNF, IL-8 and IL-17 are expressed during psoriasis.

Tumour necrosis factor. Tumour necrosis factor is the first member of the TNF cytokine superfamily. TNF is expressed as a transmembrane precursor protein. It is proteolytically cleaved into a soluble form. TNF induces intracellular signalling by binding to either p55 TNF receptor (TNFR)-1 with a nearly ubiquitous expression pattern or p75 TNFR-2 with more restricted expression by immune cells and EC. TNF leads to the activation of EC resulting in an increased expression of adhesion molecules and chemokines (Patterson *et al.* 1996). The impact of TNF on angiogenesis is dose- and time-dependent, and is influenced by the presence of other TNF-dependent factors such as VEGF or platelet-activating factor (Fajardo *et al.* 1992; Montrucchio *et al.* 1994; Patterson *et al.* 1996). TNF induces various pro-angiogenic factors, such as VEGF, IL-8 and bFGF, in EC (Yoshida *et al.* 1997) and exerts both pro- and anti-angiogenic effects. Initially, TNF was shown to inhibit EC proliferation *in vitro*, yet it stimulates neovascularization in the rabbit cornea micropocket assay *in vivo* (Frater-Schroder *et al.* 1987). TNF can be produced by almost any cell. Mast cells even store preformed TNF, which can be rapidly released by appropriate stimulation. In consequence, elevated levels of TNF mRNA and protein are detectable in psoriasis skin (Johansen *et al.* 2006). Therapies blocking the activity of TNF lead to clinical improvement of psoriasis and decreased expression of pro-angiogenic factors. The data confirm that TNF contributes to angiogenesis associated with psoriasis. It remains open whether it directly causes angiogenesis or indirectly through the induction of pro-inflammatory or angiogenic factors.

Interleukin-8. Interleukin-8 was originally isolated and characterized from scales of psoriasis (Schroder & Christophers 1986). IL-8 or CXCL8 belongs to the CXC family of chemokines, which is characterized by four highly conserved cysteins with the first two cysteins separated by a nonconserved amino acid (CXC) (Baggiolini *et al.* 1997; Rollins 1997; Brat *et al.* 2005). IL-8 is a strong chemoattractant for neutrophils, basophils and T lymphocytes, and is involved in autoimmune, inflammatory and infectious diseases (Brat *et al.* 2005). IL-8 can be induced by IL-1, TNF, IL-6, IFN-γ, lipopolysaccharides, reactive oxygen species and other mediators of cellular stress. IL-8 is also a potent pro-angiogenic factor (Koch *et al.* 1992; Strieter *et al.* 1992; Hu *et al.* 1993). The pro-angiogenic effects of IL-8 are independent of its pro-inflammatory functions as IL-8 also stimulates angiogenesis in the absence of inflammation (Strieter *et al.* 1992; Hu *et al.* 1993). IL-8 has been described to stimulate EC proliferation, migration, survival and expression of MMPs. Thus, IL-8 was shown to promote EC migration as well as

EC proliferation and tube formation of EC *in vitro* (Koch *et al.* 1992; Szekanecz *et al.* 1994; Shono *et al.* 1996; Li *et al.* 2003). Moreover, IL-8 promotes EC survival by the inhibition of EC apoptosis through induction of anti-apoptotic proteins, such as Bcl2, and down-regulation of pro-apoptotic proteins such as Bax in EC (Li *et al.* 2003). IL-8 is also capable of inducing endothelial expression and activity of MMP-2 and MMP-9. The *in vitro* described pro-angiogenic functions of IL-8 were confirmed *in vivo* by various assays (Koch *et al.* 1992; Strieter *et al.* 1992; Hu *et al.* 1993).

Various cells types are capable of producing IL-8, including immune cells such as mast cells (Biedermann *et al.* 2000), neutrophils or T cells (Gillitzer & Goebeler 2001), keratinocytes (Nickoloff *et al.* 1994) and EC (Karl *et al.* 2005). In consequence, IL-8 is up-regulated in psoriatic skin and reduced after efficient therapy (Ghoreschi *et al.* 2003b). Enhanced IL-8 and IL-8 receptor mRNA is detected within the epidermis of psoriatic lesions. Immunohistochemistry localizes IL-8 protein to suprabasal keratinocytes and neutrophils (Schulz *et al.* 1993; Duan *et al.* 2001; Gillitzer & Goebeler 2001). As IL-8 can also stimulate keratinocyte proliferation (Tuschil *et al.* 1992), IL-8 stimulates the major cell types involved in psoriasis. Yet, no study reports describe efficiency of anti-IL-8 mAbs as psoriasis therapy.

Interleukin-17. The pro-inflammatory cytokine IL-17 was originally termed cytotoxic T-lymphocyte-associated antigen-8 and renamed as IL-17A (Rouvier *et al.* 1993). Today, the IL-17 cytokine family consists of six members, IL-17A–F, which are involved in inflammatory disorders and autoimmune diseases such as psoriasis and cancer (Kolls & Linden 2004). IL-17A triggers the production of chemokines, growth factors and adhesion molecules by epithelial cells, fibroblast and EC, including IL-6, IL-8, IL-1, G-CSF, GM-CSF and ICAM-1. Thus, IL-17 enhances neutrophil accumulation and granulopoiesis. In addition, IL-17A promotes the expression of TNF and IL-1β by human macrophages (Jovanovic *et al.* 1998). The induction and production of IL-17A during $CD4^+$ or $CD8^+$ memory T-cell differentiation is regulated by a series of closely linked cytokines, including TGF-β, IL-6, IL-21 and IL-23.

Interleukin-17A is a pro-angiogenic factor (Numasaki *et al.* 2003). IL-17A can induce new vessel formation in the rat cornea micropocket assay, and IL-17A overexpressing tumour cells can induce a more rapid tumour growth with significantly enhanced tumour vascularization *in vivo* (Numasaki *et al.* 2003). *In vitro*, IL-17A has no clearly described influence on EC proliferation, but stimulates EC migration and cord formation. Moreover, IL-17A stimulates the expression of pro-angiogenic factors, including VEGF that might be, at least in part, responsible for the pro-angiogenic effects of IL-17A.

Treatment of psoriasis by anti-angiogenic regimens

As angiogenesis is closely linked with the clinical manifestation of psoriasis (Figure 4), anti-angiogenic therapies may represent promising treatment approaches (Table 2). Established systemic therapies for psoriasis, such as methotrexate or cyclosporine, TNF antagonists or inhibitors of T-cell migration, interfere with both immune activation and pro-angiogenic mediators in psoriasis. Even though it is difficult to directly prove direct anti-angiogenic effects in psoriasis patients, anti-angiogenic effects of cyclosporine A (Hernandez *et al.* 2001), methotrexate (Hirata *et al.* 1989; Yamasaki *et al.* 2003), vitamin D3 analogues (Oikawa *et al.* 1990), anti-TNF antibodies (Aggarwal *et al.* 2004; Canete *et al.* 2004; Mastroianni *et al.* 2005; Cordiali-Fei *et al.* 2006; Markham *et al.* 2006) or fumaric acid esters (Loewe *et al.* 2002) are well established. Thus, cyclosporine A, an inhibitor of T-cell activation and pro-inflammatory cytokine expression (Rao *et al.* 1997; Al-Daraji *et al.* 2002), suppresses EC migration *in vitro* and impairs neovascularization in the murine cornea micropocket assay *in vivo* (Hernandez *et al.* 2001). In T cells, cyclosporine A inhibits the transcription factors of the nuclear factor of activated T cells family (Rao *et al.* 1997; Al-Daraji *et al.* 2002), which is also involved in VEGF-mediated angiogenesis (Hernandez *et al.* 2001).

Methotrexate, an anti-proliferative compound and a potential inducer of Th2 development, inhibits EC proliferation *in vitro* and angiogenesis *in vivo* by a yet unknown mechanism (Hirata *et al.* 1989; Yamasaki *et al.* 2003).

Among the biologics, the TNF antagonists target a cytokine that exerts multiple effects on angiogenesis (Vassalli 1992). These biologics proved to be highly effective in the therapy of psoriasis after systemic application (Oh *et al.* 2000; Chaudhari *et al.* 2001; Gottlieb 2003), and simultaneously exhibit potent anti-angiogenic activities. The expression of VEGF, Ang-1, Ang-2, Tie-2 and MMP-9 as well as the number of $\alpha_v\beta3$-positive blood vessels decreases significantly during psoriasis therapy with the TNF antagonist infliximab (Cordiali-Fei *et al.* 2006; Markham *et al.* 2006). The same antibody was shown to reduce the expression of VEGF, its receptors, the numbers of $CD31^+$ cells and $\alpha_v\beta3$-expressing capillaries in the synovium during psoriasis arthritis (Canete *et al.* 2004; Mastroianni *et al.* 2005). Similar effects occur with other TNF antagonists. Thus,

Table 2 Modern biologics and small molecules targeting angiogenesis directly or by indirect pathways

		Anti-angiogenic mechanism	Clinical relevance for psoriasis
Anti-psoriatic therapeutics interacting with EC biology	Efalizumab	Inhibits the transmigration of T cells by blocking the binding of LFA-1 to ICAM-1	Approved
	Etanercept	TNF-antagonist, reduces VEGF levels	Approved
	Infliximab	TNF-antagonist, reduces VEGF, angiopoietin and Tie-2 expression	Approved
	Fumaric acid esters	Inhibit TNF-mediated nuclear entry of NF-κB p65 in ECs	Approved (in Germany)
Therapeutics directly targeting angiogenesis	Anti-IL-8	Inhibits capillary tube formation *in vitro*	No efficacy in phase IIb study
	Neovastat	Inhibits EC proliferation and the activity of specific MMPs	Phase I/II
	Sunitinib	Kinase inhibitor targeting VEGFR, PDGFR and FGFR	Case report
	Pazopanib	Kinase inhibitor targeting VEGFR, PDGFR and KIT	Phase I

LFA-1, lymphocyte function-associated antigen-1; MMPs, matrix metalloproteinases; TNF, tumour necrosis factor; ECs, endothelial cells; VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor; VEGFR, VEGF receptors; FGFR, fibroblast growth factor receptor.

TNF antagonists may impair the action of TNF on angiogenesis either directly or indirectly by impairing the induction of pro-angiogenic cytokines, such as IL-8 or IL-17, and the production of important pro-angiogenic molecules such as VEGF, Ang-1, Ang-2 or Tie-2.

The fumaric acid ester dimethylfumarate (DMF) is approved in Germany for the treatment of psoriasis. Efficacy and safety have been shown in several clinical trials (Mrowietz *et al.* 1998, 1999). DMF seems to improve psoriasis by inhibiting IL-12-mediated Th1 responses and inducing IL-4 and Th2 responses (Ghoreschi *et al.* 2003a; Ghoreschi & Rocken 2004; Litjens *et al.* 2004). DMF also acts on EC by inhibiting the TNF-mediated nuclear entry of NF-κB p65 (Loewe *et al.* 2002), thereby inhibiting TNF-induced gene expression (Loewe *et al.* 2001).

Thus, the systemic therapies currently established for the treatment of psoriasis do not only modulate the immune response of psoriasis, but also directly inhibit important mediators of angiogenesis.

As angiogenesis is a key phenomenon in the development of psoriasis, it remains open to what extent the anti-angiogenic properties of the treatments above contribute to the treatment of psoriasis. In line with this speculation, it is interesting that in a phase I/II clinical trial with Neovastat (AE-941) (Sauder *et al.* 2002), an inhibitor of EC proliferation *in vitro* and angiogenesis *in vivo* (Dupont *et al.* 2002), a dose-dependent clinical improvement of psoriasis was observed. Kinase inhibitors targeting VEGFR are used in patients with malignancies but could also be helpful in selected patients with psoriasis. Interestingly, therapy with sunitinib (SU-011248), an inhibitor of VEGFR-2, platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (Kerbel & Folkman 2002; Faivre *et al.* 2006), may improve psoriasis at least in single patients (Keshtgarpour & Dudek 2007). Topical use of VEGFR inhibitors is more promising in the setting of non-cancer patients to limit the risk of unwanted toxicities. Pazopanib, an inhibitor of VEGFR-1, -2 and -3, PDGFR and c-kit, is currently evaluated in phase II/III tumour trials (Podar *et al.* 2006; Podar & Anderson 2007), and its topical formulation is under investigation in chronic plaques psoriasis.

Prospective, controlled clinical trials are needed to evaluate the safety and efficacy of anti-angiogenic therapies with mAbs or protein kinase inhibitors in the therapy of psoriasis.

Together, the data currently available show that either the inhibition of TNF or immune deviation of T cells from a Th1/Th17 phenotype into a Th2 phenotype is most efficient in treating psoriasis. Yet, in view of most recent studies and the insights into the role of angiogenesis in psoriasis development, it is reasonable to assume that a primarily anti-angiogenic approach is highly promising as the treatment of psoriasis. In addition, such an approach should have strong anti-tumour effects and might be ideal for patients with extensive phototherapy or malignancies in their history (Weischer *et al.* 2007).

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